

ABSTRACT

MATRIX METALLOPROTEINASE INHIBITORS

5

Compounds are provided that bind allosterically to the catalytic domain of MMP-13 and comprise a hydrophobic group, first and second hydrogen bond acceptors and at least one, and preferably both, of a third hydrogen bond acceptor and a second hydrophobic group. Cartesian coordinates for centroids of the above 10 features are defined in the specification. When the ligand binds to MMP-13, the first, second and third (when present) hydrogen bond acceptors bond respectively with Thr245, Thr 247 and Met 253, the first hydrophobic group locates within the S1' channel of MMP-13 and the second hydrophobic group (when present) is relatively open to solvent. The compounds specifically inhibit the matrix 15 metalloproteinase-13 enzyme and thus are useful for treating diseases resulting from tissue breakdown, such as heart disease, multiple sclerosis, arthritis, atherosclerosis, and osteoporosis.

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100